

### REMARKS

Applicants would like to thank the Examiner for the telephone interview on July 3, 2003 ("telephone interview"). The remarks below include points discussed during the interview and serve as a summary of the interview.

During the telephone interview, the Examiner agreed to withdraw the rejection of claim 1-9 and 23-36 under 35 U.S.C. 112 first paragraph. She also suggested deleting the recitation "directly or indirectly" in claim 1. Applicants have amended claim 1, as well as claim 23, accordingly. Applicants have further amended these two claims to more clearly set forth the terms "specific binding pair" and "first binding member." Support for the recitation "if the first binding member is an oligonucleotide, it is not complementary to any part of the nucleic acid" can be found at page 2, lines 23-24. Indeed, it is an implicit limitation of original claims 1 and 23 and no new matter has been introduced.

**The amendments should be entered as they raise no new issues that will require further consideration or search and also do not touch the merits of the application within the meaning of 37 C.F.R. § 1.116(b).**

Claims 1-36 are pending. Claims 10-22 have been withdrawn from further consideration as being drawn to a non-elected invention. Claims 1-9 and 23-36 are now under examination. Reconsideration of this application is requested in view of the following remarks:

#### Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected all pending claims for containing new matter. See the Office Action, page 7, lines 12-13. Independent claims 1 and 23 respectively cover a discrimination primer having a first binding member and a kit containing such a primer. In the response filed March 4, 2003, Applicants inserted into claims 1 and 23 the recitation "the first binding member is not labeled directly or indirectly." To support this new matter rejection, the Examiner pointed out that the discrimination primer of claim 1 had a binding member. See the Office Action, page 7, lines 15-18. The Examiner has mistaken "hav[ing] a binding member" for "labeled," and, as a result, erroneously believed that the discrimination primer of claim 1 was labeled.

Applicants would like to point out that "labeled" refers to affixed with a traceable constituent (e.g., enzyme, isotope, and fluorophore). See Merriam Webster's Collegiate

Dictionary 10<sup>th</sup> edition, page 649. The specification has disclosed 2 actually prepared discrimination primers, R11-1-3mis18 (SEQ ID NO:2) and RM11-1-3mis18 (SEQ ID NO:3). Neither of them was linked with a traceable constituent, i.e., they were not labeled. See page 8, lines 5-11 of the specification. It follows that the first binding member, an element of the discrimination primer, must also not be labeled.

For the above reasons, Applicants submit that the recitation "the first binding member is not labeled directly or indirectly" does not constitute new matter and the rejection should be withdrawn. Indeed, the Examiner agreed to withdraw this rejection during the telephone interview.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner also rejected all pending claims for being indefinite. See the Office Action, page 8, lines 4-6. More specifically, the Examiner stated that the recitation "the first binding member is not labeled directly or indirectly" in claim 1 or 23 "is unclear as to whether the [discrimination] primer is labeled or not." See the Office Action, page 8, lines 7-9. As discussed above, the discrimination primer is not labeled. Thus, there is nothing indefinite about this recitation. During the telephone interview, the Examiner pointed out that the phrase "directly or indirectly" is unnecessary and suggested deleting it. Applicants have deleted the phrase and request withdrawal of this rejection.

Rejection under 35 U.S.C. § 103(a)

The Examiner maintained her rejection against all pending claims as being obvious on various grounds. Applicants will address each of the grounds below:

**I**

The Examiner maintained her rejection against claims 1-2, 5-6, 9, 23-26, 28-29, 31-32, and 34-35 as being obvious over U.S. Patent No. 6,156,503 to Drazen et al. ("Drazen") in view of U.S. Patent No. 6,383,742 to Drmanac et al. ("Drmanac"). See the Office Action, page 3, lines 5-7. Applicants respectfully traverse.

Independent claim 1 is discussed first. Claim 1 covers a discrimination primer for amplifying a nucleic acid that has a first base at a position suspected of a polymorphism and a

second base immediately 3' to the first base. Applicants have illustrated this primer and its use in Exhibit 1 (attached) and the prior art probes/primers in Exhibit 2 (also attached).

As shown in Exhibit 1A, this discrimination primer has (1) a first nucleotide located at the 3' terminus of the primer and contains a base that is complementary to the first base ("S"); (2) a second nucleotide located immediately 5' to the first nucleotide and contains a base that is not complementary to the second base ("X"); (3) a segment of nucleotides located immediately 5' to the second nucleotide and is complementary to a part of the nucleic acid that is immediately 3' to the second base; and (4) a first binding member of a specific binding pair that includes the first binding member and a second binding member. The first binding member is not labeled and is covalently bonded to the 5' terminus of the segment; the second binding member is adapted for affixation on a solid substrate. See Exhibit 1B. Use of the discrimination primer of claim 1, together with an amplification primer that is labeled at its 5' end, allows one to amplify the polymorphism-containing target nucleic acid by a polymerase chain reaction (PCR). After the PCR, one can (1) affix one end of the amplified nucleic acid onto a solid substrate via attachment of the first binding member to the second binding member already affixed on a substrate, and (2) detect the bound target nucleic acid via the labeled amplification primer incorporated into the other end of the amplified target nucleic acid. See Exhibit 1C.

In contrast, as the Examiner have correctly pointed out, Drazen teaches a primer having a mismatch at the penultimate position from its 3' end (Exhibit 2A); and Drmanac teaches a method of detecting a target nucleic acid species using a probe that is labeled with a ligand (Exhibit 2B, "Labeled probe").<sup>1</sup> See the Office Action, page 3, line 8 through page 4, line 1. A combination of Drazen and Drmanac would suggest a primer that has a mismatch at the penultimate position and a ligand that is labeled. See Exhibit 2C. This labeled primer is traceable. To the extent that Drazen and Drmanac suggest a primer having a ligand that is labeled, and thus traceable, they **teach away** from the discrimination primer of claim 1, which has a first binding member that is not labeled.

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<sup>1</sup> The Drmanac ligand serves as a binding member to a traceable constituent such as an enzyme or an antibody labeled with such a traceable constituent. Drmanac also teaches a probe affixed to a substrate (Exhibit 2B, "Affixed probe") in addition to a labeled probe. Using these two probes allows one to attach a target nucleic acid to a substrate (e.g., Covalink NH) and detect it.

The Examiner alleged that the response filed March 4, 2003 was not persuasive, since “[it] is unclear whether the first binding member is labeled...” See the Office Action, page 4, lines 16-17. As discussed above, the first binding member is clearly not labeled. The Examiner’s position is therefore based on a factually erroneous premise.

The Examiner incorrectly stated that “[t]he teaching of Drazen et al. would satisfy” the limitation “the first binding member is not labeled” in claim 1. See the Office Action, page 4, lines 12-13 and page 5, lines 1-2. The Examiner then contradicted herself and correctly pointed out that “[t]he teachings of Drazen et al. indicate that the primer is labeled.” See the Office Action, page 4, line 18. As discussed above, Drazen **teaches away** from the primer of claim 1.

Note that Drazen teaches a primer “corresponding to [a target nucleic acid] ... except the penultimate base at the 3’ end ...” See column 11, lines 16-18. In other words, all nucleotides of the Drazen primer, except the penultimate base, are complementary to the target nucleic acid. In contrast, in the discrimination primer of claim 1, “if the first binding member is an oligonucleotide, it is not complementary to any part of the [target] nucleic acid.” See the proviso in amended claim 1. Thus, the primer of claim 1 differs greatly from the Drazen primer.

In view of the remarks set forth above, claim 1 is clearly not rendered obvious by Drazen and Drmanac. Claim 23 covers a kit that includes a discrimination primer of claim 1 and is therefore also not rendered obvious by these two references for the same reasons. Neither are claims 2, 5-6, 9, 24-26, 28-29, 31-32, and 34-35, all of which depend from claims 1 and 23 directly or indirectly.

## II

The Examiner also maintained her rejection against claims 3-4, 7-8, 26, 30, 32, and 36 for being obvious over Drazen in view of Drmanac and U.S. Patent No. 5,994,056 to Higuchi et al. (“Higuchi”). See the Office Action, page 5, lines 3-6. Applicants disagree and will address claims 1 and 23 first.

Higuchi teaches primers having non-complementary sequences added to their 5’ ends (Exhibit 2D). These “tail sequences provide binding targets for specific dyes ... and, consequently, [are] useful for increasing signal strength” of amplified DNA. See column 14, lines 38-47. In other words, Higuchi teaches primers having tail sequences that are labeled directly with dyes, and therefore **teaches away** from the discrimination primer of claim 1, which

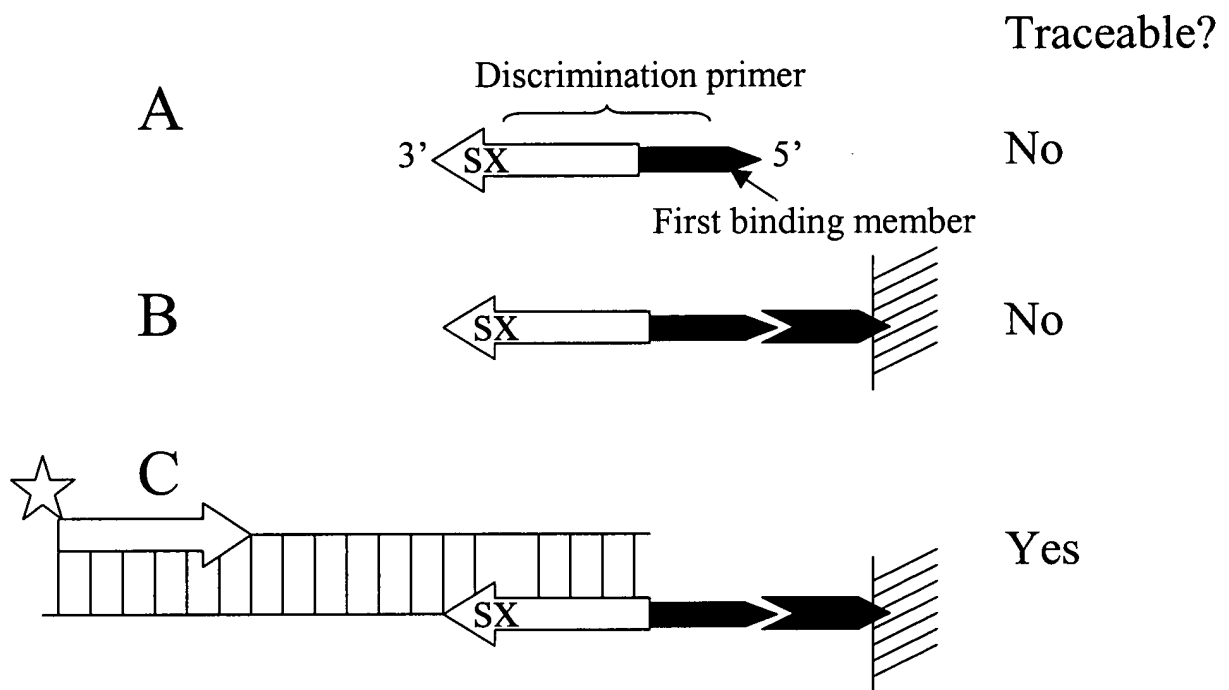
has a first binding member that is not labeled. Indeed, a combination of Higuchi, Drazen, and Drmanac would suggest a labeled primer. See Exhibit 2E.

For these reasons and those set forth above in Part I, Drazen, Drmanac, and Higuchi, alone or combined, do not render claim 1 obvious. Neither do they render obvious claim 23, which covers a kit requiring the discrimination primer of claim 1. Claims 3-4, 7-8, 26, 30, 32, and 36, all of which depend from claims 1 and 23, are also not obvious in view of these 3 references.

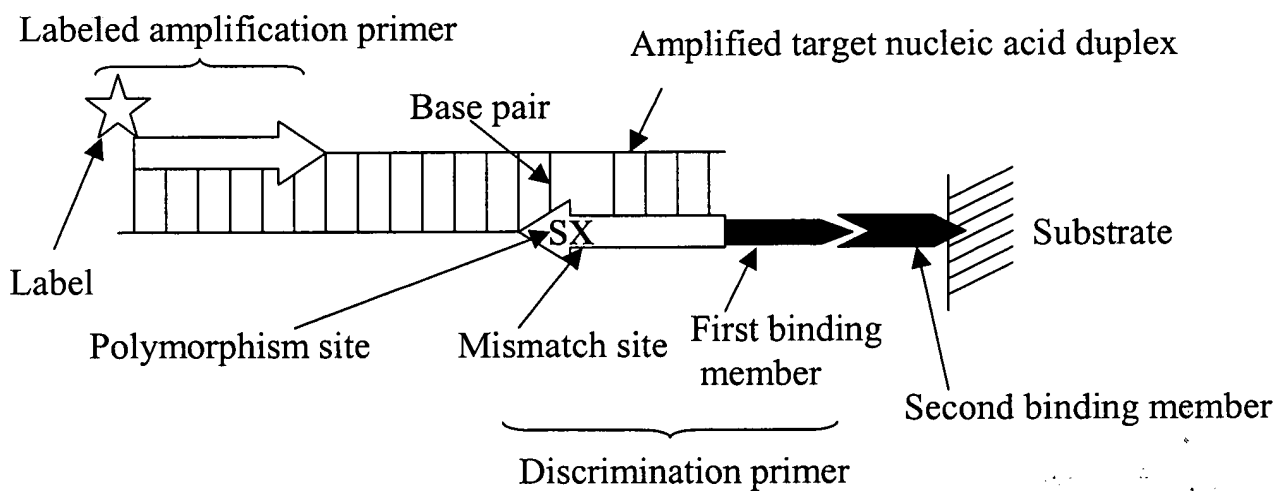
### CONCLUSION

For the above remarks, Applicants submit that the grounds for rejection asserted by the Examiner have been overcome, and the claims, as pending, define subject matter that is non-obvious, definite, and in compliance with the written description requirement. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

# Exhibit 1. Discrimination primer disclosed in this invention

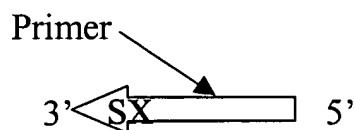


## Legend

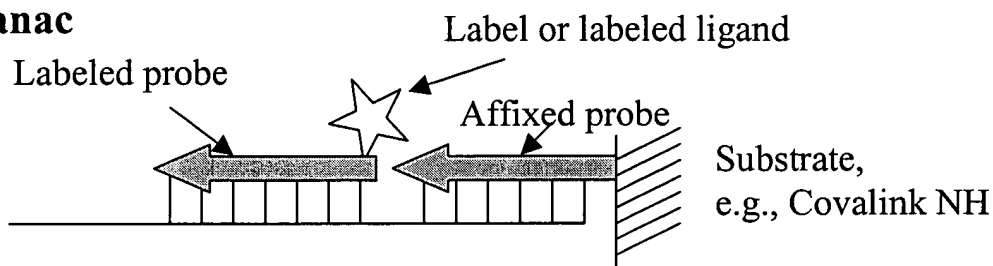


## Exhibit 2. Primers or probes taught by prior art references

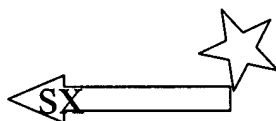
### A. Drazen



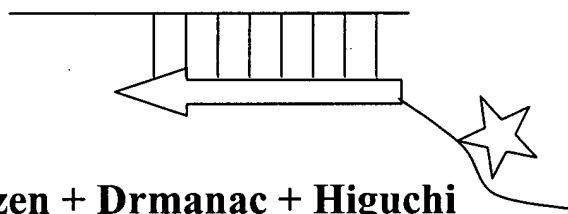
### B. Drmanac



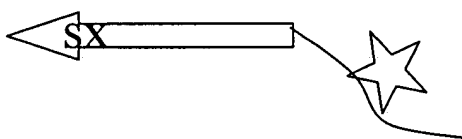
### C. Drazen + Drmanac



### D. Higuchi



### E. Drazen + Drmanac + Higuchi



### Legend

